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# Author Manuscript

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**TITLE**

Patient respiratory-triggered quantitative T2 Mapping in the pancreas

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## **RUNNING TITLE**

T2 mapping in pancreas at 3T

## **ABSTRACT**

**BACKGROUND:** Long acquisition times and motion sensitivity limit T2 mapping in the abdomen. Accelerated mapping at 3T may allow for quantitative assessment of diffuse pancreatic disease in patients during free-breathing.

**PURPOSE:** To test the feasibility of respiratory-triggered quantitative T2 analysis in the pancreas and correlate T2-values with age, body mass index, pancreatic location, main pancreatic duct dilatation and underlying pathology.

**STUDY TYPE:** Retrospective single center pilot study

**POPULATION:** Eighty-eight adults

**FIELD STRENGTH/ SEQUENCE:** Ten-fold accelerated multi-echo-spin-echo T3 magnetic resonance imaging sequence to quantify T2 at 3T.

**ASSESSMENT:** Two radiologists independently delineated three regions of interest inside the pancreatic head, body and tail for each acquisition. Means and standard deviations for T2 values in these regions were determined. T2-value variation with demographic data, intraparenchymal location, pancreatic duct dilation and underlying pancreatic disease was assessed.

**STATISTICAL TESTS:** Inter-reader reliability was determined by calculating the interclass coefficient (ICCs). T2 values were compared for different pancreatic locations by analysis of variance (ANOVA). Inter-patient associations between T2 values and demographical, clinical, and radiological data were calculated (ANOVA).

**RESULTS:** The accelerated T2 mapping sequence was successfully performed in all participants (mean acquisition time,  $2:48 \pm 0:43$  min. Low T2 value variability was observed across all patients (inter-subject) (head:  $60.2 \pm 8.3$  ms, body:  $63.9 \pm 11.5$  ms, tail:  $66.8 \pm 16.4$  ms). Inter-reader agreement was good (ICC, 0.82, 95% confidence interval: 0.77-0.86)). T2-values differed significantly depending on age ( $P < 0.001$ ), location ( $P < 0.001$ ), main pancreatic duct dilatation ( $P < 0.001$ ) and diffuse pancreatic disease ( $P < 0.03$ ).

**DATA CONCLUSION:** The feasibility of accelerated T2 mapping at 3T in moving abdominal organs was demonstrated in the pancreas since T2 values were stable and reproducible. In the pancreatic parenchyma, T2-values were significantly dependent on demographic and clinical parameters.

**KEYWORDS:**

Quantitative MRI, pancreas, T2 mapping

## INTRODUCTION

While T1- and T2- weighted imaging are the mainstay of most clinical magnetic resonance (MR) imaging (MRI) protocols, high-resolution parametric T2 maps can be clinically relevant for measuring tissue properties (1). Unlike conventional MR sequences, which evaluate morphological alterations, T2 mapping (or T2 relaxometry) enables quantification of the transverse relaxation time of the underlying tissues (2). This evaluation is assumed to be more sensitive and reproducible than the visual assessment of T2-weighted MR images for identifying minor contrast changes (e.g., tissue edema) (3). For this reason, it is applied for quantifying well-defined pathologies (e.g., cardiac iron overload or cartilage degeneration) (4, 5).

T2 mapping has been introduced into clinical practice for various organs and tissues, including brain (6–8), heart (4, 9) and cartilage (5, 10–12). In neuroradiology, a microstructural change, such as neuronal loss or demyelination, results in increased free water and thus longer T2 relaxation times and greater signal intensity on T2-weighted MRI images (13). Furthermore, T2 mapping is used to assess cartilage damage in musculoskeletal imaging (10–12) and to evaluate cardiac edema and fibrosis (9).

T2 mapping in the abdomen has proven more difficult because of movement of the abdominal organs with breathing. In addition, bowel peristalsis can result in motion artifacts. However, the technique has already been successfully applied in the liver for diffuse disease, such as iron overload (14) and cirrhosis (2, 15). Of note, in one of these reports, analysis of the left liver lobe was avoided because of motion artifact (2). Otherwise, motion as a limitation has not been addressed, mainly because of attention to analysis of diffuse parenchyma and not focal lesions.

Pancreatic T2 mapping has been successfully performed in a few healthy volunteers at 1.5 and 3T (16–18), but the technique has yet to be investigated in a patient population. Furthermore, because motion artifacts are invariably associated with long acquisition times in quantitative imaging, T2 mapping in abdominal organs has not been widely performed. However, recent work validated a novel quantitative MRI sequence for T2 mapping in the brain, that drastically shortened acquisition time compared to previously used methods (19). A similar strategy also might enable reproducible T2 mapping in moving abdominal organs.

Although pancreatic T1 mapping has already been successfully applied for assessing chronic pancreatitis (20, 21) T2 mapping in the pancreas also is of clinical interest. In acute pancreatitis, inflammatory cell recruitment induces parenchymal changes, including edema that lengthens the T2 relaxation time (22), typically observed as increased T2-weighted signal. Pancreatic T2 mapping could enable quantification of T2 changes caused by underlying edema and inflammation, offering a means of objective staging. However, before pathology can be assessed reference values need to be established, as does an overview of how findings vary with different clinical parameters.

The primary goal of this pilot study therefore was to demonstrate the feasibility of rapid and respiratory-triggered pancreatic T2 mapping to obtain reproducible T2 values. The secondary goal was to investigate quantitative differences in T2 values as they relate to age, body mass index (BMI), and sex. The third goal was to assess the correlation between pancreatic T2 values, anatomical region (head, body, tail), pancreatic duct dilatation, and underlying pancreatic disease.

## **MATERIALS AND METHODS**

### ***Study design***

This retrospective, single-center pilot study was approved by the institutional review board. Informed written consent was waived. From September 2016 to January 2017, a prototype T2-mapping MR sequence was included in our dedicated liver MR imaging protocol with the goal of improving the assessment of liver cirrhosis, particularly in case of iron overload (2, 14, 15). We reviewed all patients who underwent liver MRI with T2 mapping (n=93) and were adults (age >18 years). We excluded five of this group from the analysis. These were patients in whom the identification of the pancreas parenchyma on the MR images was impossible because of complete pancreatic fat involution (n=1) or complete surgical removal (n=1) and patients in whom the T2 mapping MRI prototype sequence had a technical problem in the image reconstruction failing to provide T2 maps (n=3). The study population thus consisted of 88 patients (46 women, 52%), with a mean age of 57 years (range: 24-93, standard deviation (SD): 17.2) and mean BMI of 24kg/m<sup>2</sup> (range: 17-39, SD: 4.1).

### ***MR data acquisition and reconstruction***

Patients underwent a conventional liver MRI examination during which the T2 mapping prototype sequence was acquired. To prevent stochastic peristaltic movement, the patients were asked to fast for 6 h before the MRI exam, and an intravenous injection of 10mg scopolamine (Buscopan ®) was administered prior to the exam. All patients were scanned in a supine position at 3T (MAGNETOM Skyra (n.=4), Skyra-Fit (n.=.75) and PrismaFit (n.=.9), Siemens Healthcare, Erlangen, Germany) using an 18-channel body array coil and a 32-channel spine coil. A multi-echo spin-echo (MESE) (23) prototype sequence was used to acquire a 10-fold undersampled k-space using Prospective Acquisition Correction (PACE) (24) with external triggering (15 slices, 0.8 × 0.8 × 5 mm resolution,  $\Delta TE/TR/TA$  10.6 ms/2.2 s/2:39 min). According to the individual trigger efficiency of a patient, the MR technician choose either a phase scout or a 1D navigator at the liver dome to trigger the acquisition on end-expiration, thus allowing free breathing for the patients. For the reconstruction of T2

maps, a combination of Generalized Auto-calibrating Partially Parallel Acquisition (GRAPPA) (25) and Model-based Accelerated Relaxometry by Iterative Non-linear Inversion (MARTINI) (26), termed GRAPPATINI (19) was employed. Furthermore, synthetic T2-weighted images with different simulated echo times ( $TE = 40/100/150\text{ms}$ ) were generated by applying the forward signal model onto the quantitative maps.

### *Data collection and analysis*

Two radiologists (NVV and SS) with 5 and 15 years of experience in abdominal MRIs, respectively, reviewed the T2 mapping sequence in all study patients. Each of the two readers separately reviewed the images on a picture archiving and communication system workstation (Carestream Vue, version 11.4; Carestream Health, Rochester, NY, USA). Patient information was masked to both radiologists during image analysis. Each radiologist determined the T2 values (mean and SD) by manually drawing one region of interest (ROI) in each head, body, and tail of the pancreatic parenchyma (**Fig.1**). The readers were instructed to draw the largest possible ROI in each area, while avoiding the pancreatic duct, vessels, focal lesions and zones showing clear partial volume effects. They repeated the same analysis 3 weeks later to reduce recall bias. Furthermore, both radiologists performed a qualitative analysis of the pancreatic parenchyma in each case by reporting any pancreatic duct dilatation, defined by a maximal diameter of  $>4\text{ mm}$ , and any sign of diffuse pancreatic disease (acute or chronic pancreatitis, pancreatic fat infiltration). The two readers discussed any discordances until they reached a consensus.

One of the readers (NVV) then reviewed electronic patient charts to collect demographic and clinical data (sex, age, BMI, and any possible diffuse/focal pancreatic disease). Finally, the acquisition time of the T2 mapping sequence was extracted from the DICOM headers.



### ***Statistical analysis***

Statistical analysis was performed with the commercially available software R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>.). The T2 values separately determined by the two radiologists were compared using an adjusted interclass correlation coefficient (ICC) to assess intra- and inter-observer reproducibility. According to Koo et al, reliability was classified as poor (ICC < 0.5), moderate (ICC between 0.5 and 0.75), good (ICC between 0.75 and 0.9), or excellent (ICC > 0.90) (27).

Furthermore, the data from the two observers were averaged for the subsequent analyses. The mean T2 value was compared in the same patient for the three pancreatic anatomical regions (head, body and tail) and across all study patients. Finally, T2 values were correlated in each patient with the corresponding demographic, clinical, and radiological data.

Categorical variables were compared using the Chi-square test, and continuous variables with the Student's t-test, or analysis of variance (ANOVA) or Pearson correlation. Statistical differences were considered significant with a  $P < 0.05$ .

## **RESULTS**

### ***MR data acquisition and reconstruction***

In all 88 patients, the pancreatic parenchyma was clearly visible in both the T2 maps and the simulated T2-weighted images (**Fig. 2**). The mean acquisition time was 2 min, 50s (range 2 min, 10s – 6min, SD: 1min 7s). The acquisition times depended mainly on patient breathing rhythm and trigger efficiency.

### ***Data collection and analysis***

Among the 88 study patients, 25 (28%) had main pancreatic duct dilation; all of chronic origin. Chronic pancreatic disease was identified in six patients (7%), either chronic pancreatitis (n = 4) or fatty involution (n = 2).

T2 values were similar across all patients (inter-subject), with low SD values (head:  $60.3 \pm 8.3$  ms, body:  $63.9 \pm 11.5$  ms, tail:  $66.8 \pm 16.4$  ms). Inter- and intra-reader reproducibility values are shown in **Table 1**. ICC was good between the two readers for the overall analyses (ICC = 0.820, 95% CI = 0.774-0.857), as well as for each anatomical location (head: ICC = 0.794, 95% CI = 0.697-0.862; body: ICC = 0.806, 95% CI = 0.715-0.870; tail: ICC = 0.836, 95% CI = 0.757-0.891). Intra-reader reproducibility was also mostly good with only three exceptions showing moderate results (**Table 1**).

**Figure 3** summarizes significant correlations between the T2 values and patient characteristics. A significant correlation was found between T2 values and age ( $r(238) = 0.347$ ;  $P < 0.001$ ). There also was a significant difference in T2 values across the anatomical locations (head:  $60.3 \pm 8.3$  ms; body:  $63.9 \pm 11.5$  ms; tail:  $66.8 \pm 16.4$  ms;  $F(2,158) = 12.566$ ;  $P < 0.001$ ) with significantly lower T2 values in the pancreas head than in the body and tail. Mean T2 values were significantly higher in patients with pancreatic duct dilatation compared to patients without main pancreatic duct dilatation (presence of dilatation:  $76.6 \pm 16.4$ , absence of dilatation:  $59.3 \pm 7.7$  ms;  $t(238) = -10.943$ ;  $P < 0.001$ ). T2 values were also significantly higher in patients with diffuse pancreatic disease compared to those with a healthy pancreas (presence of diffuse disease:  $70.7 \pm 9.2$  ms, healthy pancreas:  $63.2 \pm 13$  ms;  $t(238) = -2.187$ ;  $P < 0.03$ ). No significant correlations were found for sex (male:  $64.7 \pm 12.6$  ms, female:  $62.8 \pm 13.2$  ms,  $t(238) = 1.13$ ;  $P = 0.26$ ) and for BMI ( $r(238) = -0.063$ ;  $P = 0.335$ ).

## DISCUSSION

We demonstrated the feasibility of quantitative T2 mapping in moving abdominal organs, in particular the pancreas, with a respiratory-triggered GRAPPATINI prototype. T2 values in patients were stable and reproducible with mostly good reliability. Pancreatic T2 values varied with anatomical location (highest in the tail of the pancreas) and we found a significant correlation between T2 values and age, pancreatic duct dilatation and diffuse pancreatic disease.

De Bazelaire et al determined T1- and T2- values of various abdominal organs in six healthy volunteers, comparing results obtained at 1.5T with those at 3T (17). Pancreatic T2-values were  $46 \pm 6$  ms at 1.5T and  $43 \pm 7$  ms at 3T, both lower ranges than in the current study. Hoad et al analyzed T2 values in various abdominal organs at 3T in 10 healthy volunteers and also reported pancreatic values ( $42 \pm 20$  ms) lower than ours (18). Both groups used T2 prepared sequences with different read-out techniques: HASTE for the former and balanced steady state free precession (bSSFP) for the latter. We chose the MESE approach because T2 preparation may add further sensitivity to system imperfections, namely B1 and B0 inhomogeneity. Furthermore, a HASTE readout uses the entire echo train to sample the k-space, which will introduce T2 blurring. On the other hand, bSSFP readouts are sampling efficient but sensitive to B0 field inhomogeneity, which leads to banding artifacts. Upadhyay et al recently reported results on T2 mapping of the pancreas in 10 volunteers at 1.5-T (16). The values presented here are in line with their results (57.8 ms to 63.14 ms). Of note, they used an imaging sequence similar to the MESE sequence used here, but with different sequence parameters (resolution, TR,  $\Delta$ TE, echo-train length) and without acceleration. The reconstruction of the prototype sequence here does not account for stimulated echoes, leading to a slight T2 overestimation, as discussed previously, this effect is typical for MESE sequences (19). However, good to high reproducibility within and across participants has been demonstrated by Upadhyay et al as well as in the current study.

The scan times in this study were shorter and provided much higher resolution images with whole pancreas coverage compared to Upadhyay et al (8 min versus 2 min 50s). The sequence acquisition time depends mostly on the trigger efficiency and breathing rate of the patient. Trigger efficiency may be poor in non-cooperative patients prolonging the acquisition time. However, the mean acquisition time here was 2 min 50 s with a higher range of 6min that was still lower than in the comparative study. The faster acquisition, enabled by GRAPPATINI with high (10-fold) acceleration, is also advantageous regarding motion artifacts because bulk motion is less likely to happen during shorter acquisition times (28). Hence, GRAPPATINI may help in moving towards routine clinical applications of quantitative T2 in the abdomen.

T2 values differed with pancreatic anatomical location and were higher in the tail and lower in the head. Because no fat suppression was used, the correlation could have resulted from differences in fat infiltration among regions, with the most important region being the tail. However, this assumption seems unlikely; T2 values were lower in the head (compared to body and tail) and fat replacement occurs predominantly in the head (29). An erroneous inclusion of a slight amount of peri-pancreatic fat in the analysis also seems unlikely due to the low intra- and intra-observer variability in our values. Finally, this difference may be (partly) explained by the pancreatic cranio-caudal anatomy, with the tail being thinner than the body and head and, thus, possibly inducing more partial volume effect.

We also found a significant correlation between T2 values and age in line with previous MRI studies showing that an association between fat infiltration of the pancreatic parenchyma and aging (30). Because fat is characterized by high T2-values, progressive fat infiltration with increasing age would also be expected to correlate positively with these T2 values.

Multiple factors can explain the positive correlation between pancreatic duct dilatation and T2 values. In this study, all main pancreatic duct dilatations were of chronic origin. Chronic main duct dilatation causes atrophy of the adjacent pancreatic parenchyma followed by increasing

fat infiltration (31). This set-up would be expected to lead to higher T2-values because no fat suppression was used. Kashiwagi et al reported a correlation between intraductal papillary mucinous neoplasm (a premalignant condition caused by papillary proliferation of pancreatic duct epithelium) and pancreatic fat content, suggesting that fat infiltration could be a risk for developing this neoplasm (32).

Atrophy and consecutive fat infiltration may also explain the higher T2 values with diffuse and chronic pancreatic disease (31).

In the current study, we found no correlation between T2 and sex, nor T2 and BMI. Saisho et al also reported no association of T2 with sex or age, obesity, or fat/parenchyma ratio (with only a slight difference in the pancreatic volume between males and females), in line with our results (33). Two other studies that evaluated pancreatic fat content found no correlation between pancreatic fat infiltration and BMI (or visceral fat area) as well (32, 34). This suggests that pancreatic fat infiltration is more caused by aging and atrophy than by obesity or sex.

This study has several limitations. First, as discussed above, we did not use fat suppression, so T2 values may reflect underlying fat infiltration of the pancreas. However, current fat suppression techniques are imperfect and often result in heterogeneous suppression; for this reason, they can introduce bias depending on the spatial performance of the fat suppression. Second, some patients had diffuse liver disease implying a selection bias towards this population. However, this study is the first to report pancreatic T2 values in a patient population that are in agreement with previously reported values using the same sequence (16). The third limitation is that the classification into healthy or pathologic pancreatic parenchyma was based on imaging features with no pathological reference standard. This classical limitation also occurs in patients with acute or chronic pancreatitis because the diagnosis is rarely based on pathology. We also made no comparison between different types

of pancreatic diseases and patients with chronic pancreatitis or fat infiltration because of the low number of patients with pancreatic disease. A larger study population with pancreatic disease would be of great interest for quantitative MRI and could allow edema assessment using T2 mapping. Because of the retrospective study design, we could not perform a scan and re-scan analysis, but this analysis has been done already in volunteers with high reproducibility (19).

As an alternative to T2 mapping, the apparent transverse relaxation  $T2^*$  may be accessed instead using multiple gradient echo (GRE) breath-hold acquisitions. We choose the spin-echo T2 relaxation over the GRE  $T2^*$  because local field inhomogeneity also affects  $T2^*$ . This local inhomogeneity can originate from tissue susceptibility e.g. from iron deposition. However,  $T2^*$  mapping is also sensitive to  $B_0$  field inhomogeneity and leads to local overestimation if not correctly addressed. Although  $T2^*$  may be interesting for iron-related disease such as hemochromatosis, here we were investigating mostly inflammation, which we expect to affect the T2 relaxation.

In conclusion, this study showed the feasibility of accelerated T2 mapping at 3T in moving abdominal organs, in particular the pancreas. T2 values were reproducible within and between patient with moderate to good intra- and inter-observer agreement. In the pancreatic parenchyma, T2 values varied significantly depending on age, anatomical location, presence of pancreatic duct dilatation and diffuse disease. The potential for quantitative analysis in the abdomen is of great interest and should be further investigated.

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## TABLES

**Table 1: Inter- and intra-observer reproducibility (ICC (95%CI))**

	<b>Whole pancreas</b>	<b>Pancreatic head</b>	<b>Pancreatic body</b>	<b>Pancreatic tail</b>
<b>Inter-observer reproducibility</b>	0.820 (0.774-0.857)	0.794 (0.697-0.862)	0.806 (0.715-0.870)	0.836 (0.757-0.891)
<b>Intra-observer reproducibility – 1st radiologist</b>	0.742 (0.680-0.793)	0.542 (0.369-0.679)	0.736 (0.619-0.821)	0.880 (0.820-0.921)
<b>Intra-observer reproducibility – 2nd radiologist</b>	0.864 (0.829-0.893)	0.854 (0.782-0.903)	0.837 (0.758-0.891)	0.880 (0.820-0.921)

Abbreviations: ICC: Interclass correlation coefficient, CI: Confidence Interval

## FIGURES LEGENDS

**Figure 1:** An axial T2 map depicting the pancreas in one study patient. Each radiologist determined pancreas T2 values by manually drawing regions of interest in the head, body and tail of the pancreatic parenchyma, giving the mean T2 value in each region of interest, including corresponding standard variation.

**Figure 2:** (A) Axial T2 map depicting the pancreas in one study patient. Visual inspection enabled clear delineation of the pancreatic parenchyma (arrows), including the main duct (arrowhead). Multiple synthetic reconstructions of T2-weighted images could be achieved at different TE times (B at 40 ms, C at 100 ms and D at 150 ms).

**Figure 3:** Histograms and charts of the statistically significant correlations between mean T2 values and patient characteristics. (Age (A), pancreatic anatomical regions (B), presence of main pancreatic duct dilatation (C) and presence of diffuse pancreatic disease (F)).